Clinical Cancer Research 2014 vol.20 N1, pages 28-34

Molecular pathways: Sterols and receptor signaling in cancer

Gabitova L., Gorin A., Astsaturov I.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Accelerated cholesterol and lipid metabolism are the hallmarks of cancer and contribute to malignant transformation due to the obligatory requirement for cholesterol for the function of eukaryotic membranes. To build new membranes and maintain active signaling, cancer cells depend on high intensity of endogenous cholesterol biosynthesis and uptake of lipid particles. This metabolic dependency of cancer cells on cholesterol and other lipids is tightly regulated by the cholesterol homeostasis network, including (i) sterol response element-binding proteins (SREBP), master transcriptional regulators of cholesterol and fatty acid pathway genes; (ii) nuclear sterol receptors (liver X receptors, LXR), which coordinate growth with the availability of cholesterol; and (iii) lipid particle receptors, such as low-density lipid particle (LDL) receptor, providing exogenous sterol and lipids to cancer cells. In addition, activity of oncogenic receptors, such as MUC1 or EGFR, accelerates sterol uptake and biosynthesis. Therefore, a general strategy of reducing the cholesterol pool in cancer cells is challenged by the highly efficient feedback loops compensating for a blockade at a single point in the cholesterol homeostatic network. Besides the well-established structural role of cholesterol in membranes, recent studies have uncovered potent biologic activities of certain cholesterol metabolic precursors and its oxidized derivatives, oxysterols. The former, meiosis-activating sterols, exert effects on trafficking and signaling of oncogenic EGF receptor (EGFR). Cholesterol epoxides, the highly active products of cholesterol oxidation, are being neutralized by the distal sterol pathway enzymes, emopamyl-binding protein (EBP) and dehydrocholesterol-7 reductase (DHCR7). These recently discovered "moonlighting" activities of the cholesterol pathway genes and metabolites expand our understanding of the uniquely conserved roles these sterol molecules play in the regulation of cellular proliferation and in cancer. Clin Cancer Res; 20(1); 28-34. © 2013 AACR.

http://dx.doi.org/10.1158/1078-0432.CCR-13-0122